UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/684,268	10/10/2003	Felix A. Montero-Julian	2512.0230001(2147-183CIP)	1728

64562 7590 05/28/2009

STERNE KESSLER GOLDSTEIN & FOX, P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
05/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/684,268	MONTERO-JULIAN ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68,69,72 and 74-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68,69,72 and 74-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/17/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 2/17/09 is acknowledged and has been entered.

Claims 68, 69, 72, 76, 78 and 80-85 read upon the elected Group and species.

Applicant is reminded that upon consideration of the prior art, the species in claim 77 and the species of HLA-B*0702 recited in claim 79 were also being included in examination.

Claims 68, 69, 72 and 74-86 are presently being examined.

2. Applicant's amendment filed 2/17/09 has overcome the prior rejection of record of claims 70-73 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

3. The use of the trademark STREP-TACTIN has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 86 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not supported by the originally filed disclosure is as follows:

The limitations recited in instant claim 86, "wherein for a first period of time a first peptide is bound to said chimeric MHC class I monomer and for a second period of time a second MHC binding peptide is bound to said chimeric MHC class I monomer".

Applicant does not point to support for this newly added claim.

6. Applicant's amendment filed 2/17/09 has overcome the prior rejection of record of claims 81 and 82 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 68, 69, 72 and 74-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 68 contains the trademark/trade name STREP-TACTIN. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a mutated streptavidin molecule and, accordingly, the identification/description is indefinite.

b. Claim 86 is indefinite in the recitation of "The system of claim 68, wherein for a first period of time a first peptide is bound to said chimeric MHC class I monomer and for a second period of time, a second MHC binding peptide is bound to said chimeric MHC class I monomer, wherein at all periods of time the solid surface is attached to said chimeric MHC class I monomer" because it is not clear what is meant. Claim 68 is drawn to a "system" that is a product, not a method (see for instance abstract, [0016], [0018][0076]-[0081], [0083], [0084], [0086], [0088]-[0091], [0093], [0094], claims of the US 20040137537 A1 publication of the instant application).

9. For the purpose of prior art rejections, the filing date of the instant claims 86 is deemed to be the filing date of the instant application, *i.e.,* 10/10/03, as the parent application does not support the claimed limitations of the instant application as enunciated at item #5 supra.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 68, 69, 72, 74-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Denkberg *et al* (PNAS USA, 7/02, 99(14): 9421-9426) in view of Alexander *et al* (J. Immunol. 1997, 159: 4753-4761, of record) and WO 01/90747 A2 (IDS reference in Form 1449 filed 7/1/08).

This new ground of rejection is necessitated by Applicant's amendment filed 2/17/09.

Denkberg *et al* teach a system comprising an ELISA microtiter plate coated with BSA-biotin, followed by streptavidin, followed by biotinylated MHC (HLA-A2, *i.e.,* human MHC class I monomer)/β2m/peptide complexes (the biotin attached to the C-terminal end of the monomer), and further comprising W6/32 mAb which binds HLA complexes only when folded correctly and when it contains peptide bound in the HLA binding site, or with purified Fab clones (mAb) that recognize HLA-A2 bound to a specific peptide. Denkberg *et al* teach that their system is useful for isolating and studying human recombinant Fab antibodies that exhibit a characteristic TCR-like binding specificity to HLA-A2 complexes bound to one of three recombinant peptide epitopes (see entire reference, especially first full paragraph at column 2 on page 9422 and the paragraph spanning columns 1-2 on page 9423, and abstract).

Denkberg *et al* do not teach wherein the MHC class I monomer comprises a human MHC class I domain and a murine MHC class I domain, nor that the MHC molecule bound to the solid support is comprised in a kit.

Alexander *et al* teach a chimeric MHC class I molecule comprising human HLA-A11 α1α2 domains with a murine H-2K^b α3 domain. Alexander *et al* teach that these constructs were expressed in mice, thus making transgenic mice, and that it is necessary to use the murine α3 domain in order to preserve the species-specific interactions between CD8 positive T cells in the transgenic mice [that interact with class I] and the α3 domain of the class I molecule.

WO 01/90747 A2 teaches biotinylated MHC class I monomers comprising the α1α2 and α3 domains, β2m, and optionally an antigenic peptide, bound to a solid surface such as a bead or microtiter plate, through interaction with avidin or streptavidin. WO 01/90747 A2 teaches that the MHC molecule can consist of a complex in which the presenting peptide is loaded into the binding site or it can be empty; likewise, it can be a complex of heavy chain and β2m, or be a single chain molecule. WO 01/90747 A2 further teaches using the immobilized monomers to study T cell binding to MHC class I and for detecting agents that can modulate said binding. WO 01/90747 A2 teaches kits comprising the MHC molecules, such as HLA-A2 and HLA-B7, for diagnosis or research (see entire reference, for example, abstract, lines 23-29 on page 7, lines 5-26 on page 13, lines 20-31 on page 14, paragraph spanning pages 29-30, lines 4-21 on page 51, lines 9-10 on page 53, lines 4-9 on page 54, and claims, especially claims 1, 124, 127, 130-132).

It would have been prima facie obvious to modify the system taught by Denkberg *et al* by substituting the transgenic class I construct taught by Alexander *et al* for the human class I construct taught by Denkberg *et al*, and to have used the chimeric MHC class I molecule either as a single chain construct or one that consists of heavy chain α1-α3 domains and β2m, empty or occupied with peptide as taught by WO 01/90747 A2.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to study transgenic T cells and agents that interfere with binding of those T cells to the transgenic HLA/H-2K^b class I molecule.

It would have been prima facie obvious to have included the MHC molecule bound to the solid support in a kit such as the kit taught by WO 01/90747 A2.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 01/90747 A2 teaches placing the MHC class I molecule in a kit for diagnostic or research purposes, and for the sake of convenience.

It would have been prima facie obvious to have provided the MHC bound to a solid support in a dried form.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this for convenience of handling and storage.

With regard to the limitation recited in instant claim 86, it is an expected property of (peptide) occupied MHC molecules that given the binding of MHC to peptide is a noncovalent, reversible interaction, absent evidence to the contrary, that the MHC molecules would be capable of releasing peptide and renaturing to re-incorporate peptide.

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record in the amendment filed 2/17/09 on pages 8-17 and concern the prior rejection of record, briefly: (1) the cited references fail to teach or suggest the claimed invention and provide no apparent reason to combine the references, (2) the art references do not teach the invention as presently claimed invention, (3) the linkage in the presently claimed invention allows the monomer to remain attached to the surface under denaturing conditions, and peptide exchange under these conditions is an unexpected and surprising outcome of the claimed invention, (4) Applicant argues limitations not presently in claim 81, (5) Applicant argues that OSA would not have placed the solid support in a kit or provided it in dried form, but does not present an argument as to why not.

However, the combination of references presently applied to the invention as currently claimed teaches the claimed invention; they teach the same linkage system, and motivation to combine the references to arrive at the claimed invention is enunciated supra. In addition, Applicant is arguing the references separately. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

12. Claims 68, 69, 72, 74-78, 80-84 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Denkberg *et al* (PNAS USA, 7/02, 99(14): 9421-9426) in view of Alexander *et al* (J. Immunol. 1997, 159: 4753-4761, of record) and US 5,635,363 (of record).

This new ground of rejection is necessitated by Applicant's amendment filed 2/17/09.

Denkberg *et al* teach a system comprising an ELISA microtiter plate coated with BSA-biotin, followed by streptavidin, followed by biotinylated MHC (HLA-A2, *i.e.,* human MHC class I monomer)/β2m/peptide complexes (the biotin attached to the C-terminal end of the monomer), and further comprising W6/32 mAb which binds HLA complexes only when folded correctly and when it contains peptide bound in the HLA binding site, or with purified Fab clones (mAb) that recognize HLA-A2 bound to a specific peptide. Denkberg *et al* teach that their system is useful for isolating and studying human recombinant Fab antibodies that exhibit a characteristic TCR-like binding specificity to HLA-A2 complexes bound to one of three recombinant peptide epitopes (see entire reference, especially first full paragraph at column 2 on page 9422 and the paragraph spanning columns 1-2 on page 9423, and abstract).

Denkberg *et al* do not teach wherein the MHC class I monomer comprises a human MHC class I domain and a murine MHC class I domain, nor that the MHC molecule bound to the solid support is comprised in a kit.

Alexander *et al* teach a chimeric MHC class I molecule comprising human HLA-A11 α1α2 domains with a murine H-2K^b α3 domain. Alexander *et al* teach that these constructs were expressed in mice, thus making transgenic mice, and that it is necessary to use the murine α3 domain in order to preserve the species-specific interactions between CD8 positive T cells in the transgenic mice [that interact with class I] and the α3 domain of the class I molecule.

US 5,635,363 discloses a system comprising a solid surface such as beads or a microtiter plate) to which is attached one or more biotinylated MHC monomers (*i.e.,* biotinylated at the carboxy-terminus) through interaction with streptavidin or avidin, and its use for detecting and/or separating antigen-specific T cells. US 5,635,363 discloses using the α1α2 and α3 domains of MHC heavy chain of class I molecules such as HLA-

A, -B or –C, as well as the β2m light chain. The two subunits may be combined with an antigenic peptide(s) or the peptide(s) may be added later. US 5,635,363 discloses that the T cells may be from any source, usually having the same species of origin as the MHC heterodimer (see entire reference, for example, abstract, column 1 at lines 55-67, paragraph spanning columns 4-5, column 6 at lines 51-65, column 7 at lines 12-15, column 8 at lines 4-8).

It would have been prima facie obvious to modify the solid support taught by Denkberg *et al* by substituting the transgenic class I construct taught by Alexander *et al* for the human class I construct taught by Denkberg *et al*, or with another chimeric MHC class I allele molecule (such as a different HLA-A, -B, or -C molecule, *e.g.,* HLA-A2), including as separate heavy and light chains (*i.e.,* HLA heavy chain and β2m) as disclosed by US 5,635,363.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to study transgenic T cells and agents that interfere with binding of those T cells to the transgenic HLA-A11/H-2K^b class I molecule, particularly in light of the disclosure of US 5,635,363 to use the MHC monomers to detect and/or separate antigen-specific T cells.

With regard to the limitation recited in instant claim 86, it is an expected property of (peptide) occupied MHC molecules that given the binding of MHC to peptide is a noncovalent, reversible interaction, absent evidence to the contrary, that the MHC molecules would be capable of releasing peptide and renaturing to re-incorporate peptide.

It would have been prima facie obvious to have provided the MHC bound to a solid support in a dried form.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this for convenience of handling and storage.

Applicant's arguments have been fully considered but are not persuasive.

Applicant's said arguments are of record in the amendment filed 2/17/09 on pages 17-21 and concern the prior rejection of record, briefly: (1) the cited references fail to teach or suggest the claimed invention and provide no apparent reason to combine the references, (2) the art references do not teach the invention as presently claimed, (3) the linkage in the presently claimed invention allows the monomer to remain attached to the surface under denaturing conditions, and peptide exchange under these conditions is an unexpected and surprising outcome of the claimed invention, (4) Applicant argues limitations not presently in claim 81, (5) Applicant argues that OSA would not have placed the solid support in a kit or provided it in dried form, but does not present an argument as to why not.

However, the combination of references presently applied to the invention as currently claimed teaches the claimed invention; they teach the same linkage system, and motivation to combine the references to arrive at the claimed invention is enunciated supra. In addition, Applicant is arguing the references separately. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

13. Claims 79 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Denkberg *et al* (PNAS USA, 7/02, 99(14): 9421-9426) in view of Alexander *et al* (J. Immunol. 1997, 159: 4753-4761, of record) and US 5,635,363 (of record) claims 68, 69, 72, 74-78, 80-84 and 86 above, and further in view of US 4,208,479 (of record).

This new ground of rejection is necessitated by Applicant's amendment filed 2/17/09.

Denkberg *et al*, Alexander *et al,* US 5,635,363 have been discussed supra. Alexander *et al* also teach a chimeric MHC class I molecule comprising human HLA-A2.1 (*i.e.,* HLA-A*0201) $\alpha 1 \alpha 2$ domains with a murine H-$2K^b$ $\alpha 3$ domain. Alexander *et al* teach HLA-B class I molecules (especially introduction section).

The combination of Denkberg *et al*, Alexander *et al,* US 5,635,363 does not teach that the solid support comprising the MHC class I molecule is in a kit.

US 4,208,479 discloses that reagents for performing assays may be provided in dry form, the advantages of which are their stability, shelf life and convenience over wet forms. US 4,208,479 further discloses that in performing assays, it is a matter of substantial convenience to provide the needed reagents in a kit (especially column 2 at lines 49-54, column 22 at lines 36-39 and column 22 at lines 20-68).

It would have been prima facie obvious to have included the MHC molecule bound to the solid support taught by the combination of Denkberg *et al*, Alexander *et al,* US 5,635,363 in a kit, including chimeric MHC class I molecules of the classes taught by Alexander *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because US 5,635,363 teaches placing the MHC class I molecule in a kit and for convenience.

It would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have provided the system taught by the combined references in dried form.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because US 4,208,479 discloses the advantages of providing reagents in dried form.
Claim 79 is included in this rejection because HLA-B*0702 is a subtype of the HLA-B7 class I molecule taught by Alexander *et al*.

14. Claim 68 is objected to because of the following informality: Claim 68 contains a spelling error, *i.e.,* "streptactin" rather than "STREP-TACTIN". Appropriate correction is required.

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
May 12, 2009

/G.R. Ewoldt/
Primary Examiner, Art Unit 1644